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REMARKS

Applicant notes that the election of the Claims in Group I (Claims 1, 4-9, and 13-17) made in the Response dated April 20, 2001, has been recorded. Thus, Claims 1, 4-9, and 13-17 were pending in the present application. Applicant added dependent Claims 18-21 in the Response faxed May 15, 2002. The Examiner has withdrawn Claims 2, 3 and 10-12, as being directed to a non-elected Group. In the present Response, Claims 16-19 have been cancelled without prejudice and new Claims 22 and 23 have been added. These new Claims are directed toward the CP1 nucleic acid and amino acid sequences. As these Claims find more than sufficient support in the Specification, these Claims do not contain new matter. Thus, Claims 1, 4-9, and 13-15, 20-23 are currently pending. Applicants note that the Examiner did not enter the amendments submitted in the Response to Final Office Action mailed September 30, 2002. Thus, Applicants respectfully request that the amendments presented herein with the accompanying Request for Continued Examination (RCE) be entered.

Applicant note that the Examiner has indicated that some references included in the PTO-1449 form have not been entered into this case. As these references were included solely to show the state of the art in general, Applicant is not submitting these references for the Examiner to enter into the record. As the Examiner is likely well-aware, these references provide techniques and other general information known to those in the art.

While the Examiner has removed multiple objections, one objection to the recitation of "wpr protease" in Claims 15, 17 and 21, has been maintained. The "wpr" abbreviation refers to "cell wall associated" protease. Applicant submits that the wpr protease referred to in the present Specification is the same as the "wprA" enzyme described in Margot *et al.* (Margot *et al.*, Microbiol. 142:3437-3444). Thus, Applicant submits that the terminology in the Claims is definite. Applicant notes that in the pending Advisory Action, the Examiner admits that the term is definite.

The Examiner has also objected to Claim 13 as being grammatically incorrect. Applicant appreciates the Examiner's suggestion and have amended the Claim to correct the grammar in the Claim. The Examiners rejections of the Claims are addressed in the order below:

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- 1) Claims 20 and 21 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;
- 2) Claims 16-19 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement;
- 3) Claims 1, 4-9, and 13-21 remain rejected under 35 U.S.C. §112, first paragraph as allegedly not meeting the enablement requirement; and
- 4) Claims 1, 4-9, and 13-21 remain rejected under 35 U.S.C. §102(b) as allegedly being anticipated by WO89/10976;

1) The Claims Are Definite

The Examiner has rejected Claims 20 and 21 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicant has amended the Claims without prejudice in order to more clearly indicate that SEQ ID NO:1 corresponds to the gene encoding cysteine protease 1 (SEQ ID NO:2). Applicant believes that the Claims are in condition for allowance and respectfully request that this rejection be withdrawn. Applicant notes that in the present Advisory Action, the Examiner indicates that the Claims would overcome the rejection upon entry.

2) The Present Specification and Claims Meet the Written Description Requirement

The Examiner has maintained his rejection of Claims 16-19 under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement. While Applicant must respectfully disagree, in order to further the prosecution of the present application and Applicant's business interests, yet without acquiescing to the Examiner's arguments, Applicant has cancelled Claims 16-19. Applicant reserves the right to pursue these Claims in another application. As these Claims have been cancelled, this rejection is moot and Applicant respectfully requests that this rejection be withdrawn. Applicant notes that in the present Advisory Action, the Examiner indicates that the Claims would overcome the rejection upon entry.

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3) The Present Specification and Claims Meet the Enablement Requirement

The Examiner has maintained his rejection of Claims 1, 4-9, and 13-21 under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement. More particularly, the Examiner argues that the Specification does not support the broad scope of the Claims. The Examiner argues that the Specification does not establish:

- A) regarding claims 16 and 17, the sequences of CP1 polypeptides or encoding polypeptides of all gram positive microorganisms, guidance for isolating said sequences from all gram-positive microorganisms, or the predictability that a CP1 gene is present in all gram-positive microorganisms;
- B) regions of a CP1 from any gram-positive microorganism, the polypeptide of SEQ ID NO:2, or the polynucleotide of SEQ ID NO:1 that may be mutated with an expectation of obtaining the desired biological activity;
- C) regions apr, npr, epr, wpr and mpr from all gram-positive microorganisms or *Bacillus* hosts that may be mutated with an expectation of obtaining the desired biological activity;
- D) the predictability that all gram-positive microorganisms or *Bacillus* hosts will possess a gene encoding SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1 as an undue amount of experimentation would be required to examine all gram-positive microorganisms for the presence of a gene encoding SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1; and
- E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Applicant must respectfully disagree with the Examiner's arguments. With regard to argument A), Applicant submits that the CP1 polypeptide sequences and nucleic acid sequences encoding CP1 polypeptide are indeed disclosed in the Specification as SEQ ID NO:2 and SEQ ID NO:1. Applicant further submits that there is no requirement that Applicant provide predictability as to whether all gram-positive microorganisms contain CP1. The Claims are only directed towards those microorganisms that DO contain CP1. Nonetheless, as indicated above, Claims 16 and

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17 have been deleted without prejudice. Therefore, this rejection is moot as to these Claims.

In regard to arguments B and C), Applicant submits that any mutation or deletion that results in the inactivation of CP1 proteolytic activity alone, or in combination with mutations or deletions in apr, npr, epr, wpr, and/or mpr is intended. Applicant is not required to provide each and every mutation or deletion that would result in inactivation. The Specification as filed provides means to identify CP1, as well as the nucleic acid and amino acid sequences of CP1, and means to assess proteolytic activity (See, pages 5-9 and 12). The additional proteins are known in the art (See e.g., page 9).

In regard to D), Applicant submits that there is no requirement that Applicant show the predictability that all gram-positive microorganisms or *Bacillus* hosts will possess a gene encoding SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1. Applicant respectfully submits that no undue amount of experimentation would be required to examine gram-positive microorganisms of interest for the nucleic acid sequence of SEQ ID NO:1, or the amino acid sequence of SEQ ID NO:2. Indeed, the present Specification provides means to determine the homology between the CP-1 of SEQ ID NO:1 and other sequences (See e.g., page 12). Furthermore, the amino acid sequence of SEQ ID NO:2 would be relatively easy to compare with other proteases.

In regard to E), Applicant is unsure as to what the Examiner is referring to in the clause "which of the essentially infinite possible choices is likely to be successful." Thus, Applicant cannot address this argument.

Nonetheless, in order to further the prosecution of the present application and Applicant's business interests, yet without acquiescing to the Examiner's arguments, Applicant has amended Claims 1, 13, and 14, and cancelled Claims 4 and 5. With regard to Claim 13, Applicant submits that the *Bacillus* host cell may be any species of *Bacillus*, as this Claim is directed toward transformed cells. Support for these amendments is provided throughout the Specification and no new matter has been added. Applicant reserves the right to pursue the originally filed, similar and/or broader Claims in another application(s). Applicant respectfully submits that the pending Claims are in condition for allowance and request that this rejection be withdrawn.

Although Applicant believes that all of these Claims, including those cancelled herein are enabled, in order to further the prosecution of the present application and Applicant's business interests, and without acquiescing to the Examiner's rejections,

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Applicant has cancelled Claim 14 and amended Claim 13 to recite *Bacillus subtilis*. Applicant reserves the right to pursue the originally filed and/or similar Claims in one or more additional applications.

3) **The Claims are Novel**

The Examiner has maintained his rejection of Claims 1, 4-9, and 13-17, under 35 U.S.C. §102(b) as being allegedly anticipated by WO 89/10976. The Examiner argues that "applicants have provided no evidence to distinguish CP1 or the polypeptide of SEQ ID NO:2 encoded by SEQ ID NO:2 from the cysteine protease of WO89/10976 nor have applicants distinguished the cysteine protease-deficient AP⁻/NP⁻ *B. subtilis* mutant of WO89/10976 from the claimed microorganisms . . . While applicants have amended independent claims 1, 13, 18, and 20 to recite the limitation of SEQ ID NO:2 or SEQ ID NO:1, this limitation does not distinguish the claimed microorganisms and methods of use thereof from the cited prior art as the cysteine protease-deficient AP⁻/NP⁻ *B. subtilis* of the prior art would inherently have a mutated sequence of SEQ ID NO:1 due to homologous recombination resulting in inactivation of cysteine protease activity." (Office Action, pages 7-8). Applicant must respectfully disagree. Although the Examiner has indicated that this rejection has been withdrawn, Applicant reiterates the arguments presented in the Response to Final mailed September 30, 2002, in order to ensure that these arguments are made of record in the present case.

WO 89/10976 teaches a *B. subtilis* strain that is deficient in **both** alkaline protease and neutral protease, as well as a sulfhydryl-dependent *residual* cysteine protease and/or a *residual* serine protease activities. These residual proteases are described as providing residual protease activity in *Bacillus* strains that are apr⁻/npr⁻, and are responsible for the degradation of proteins in cultures of *B. subtilis*.

As previously indicated, there is no teaching in WO 89/10976 of an organism with a mutation or deletion of part or all of the gene encoding CP-1. Indeed, there is no sequence information provided in this publication for any cysteine protease. Applicant submits that the Examiner has provided no evidence that what is described in WO89/10976 is the same as the sequence set forth in SEQ ID NOS: 1 or 2. Indeed, since there are no sequences of any cysteine protease disclosed in WO89/10976, there is no evidence that can support the Examiner's argument. A search of Genbank for each of the inventors named on WO89/10976 failed to identify any sequence

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information submitted by any of the named inventors regarding a cysteine protease from *B. subtilis*. Furthermore, a search of the Merops database provided numerous cysteine proteases from *B. subtilis*, any of which could conceivably be the same as the WO89/10976 putative cysteine protease. A copy of this printout is attached hereto.

Applicant respectfully submits that:

"[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)." (MPEP 2122, *emphasis original*).

Furthermore, Applicant respectfully submits:

"[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-151 (Fed. Cir. 1999)." (MPEP 2112).

Thus, Applicant respectfully submits that there is simply no teaching nor suggestion in WO 89/10976 of the CP1 of the presently claimed invention. Likewise, there is no teaching in WO 89/10976 of an organism with such a mutation or deletion in CP-1, as well as mutation(s) and/or deletion(s) in at least one of the genes encoding apr, npr, epr, wpr, and/or mpr. Thus, WO 89/10976 does not teach each and every element of the Claims¹, a requirement for a reference to be anticipatory. Nonetheless, in order to further the prosecution of the present application and Applicant's business interests, yet without acquiescing to the Examiner's arguments, the independent Claims have been amended to recite SEQ ID NO:2. Applicant reserves the right to pursue the originally filed and/or broader Claims in other application(s). Applicant respectfully

¹ "Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention." *RCA Corp. v. Applied Digital Data Sys., Inc.*, 730 F.2d 1440, 221 USPQ 385, 388 (Fed. Cir. 1984).

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requests that this rejection be withdrawn and the Claims passed to allowance. Indeed, as indicated in the Advisory Action, the rejection has been withdrawn.

CONCLUSION

All grounds of rejection and objection of the Final Office Action of January 22, 2002, and the Advisory Action of October 17, 2002, having been addressed, reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned.

Respectfully submitted,

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APPENDIX I
MARKED-UP VERSION OF SPECIFICATION'S REPLACEMENT PARAGRAPHS AND
REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

The following is a marked-up version of the Specification's replacement paragraphs pursuant to 37 C.F.R. §1.121(b), as well as a marked-up version of the Claims pursuant to 37 C.F.R. §1.121 (c)(1)(ii) with instructions and markings showing changes made herein to the previous version of record of the specification and claims. Underlining denotes added text while bracketing denotes deleted text.

IN THE CLAIMS:

Please cancel Claims 4, 5, 14, and 16-19.

Please amend the Claims as follows:

1. (Twice Amended) A *Bacillus subtilis* having a mutation or deletion of part or all of the gene encoding cysteine protease-1 CP1, wherein said gene encodes the amino acid sequence set forth in SEQ ID NO:2, and said mutation or deletion results in the inactivation of the CP1 proteolytic activity.

6. (Twice Amended) The *Bacillus subtilis* of Claim 1, wherein said microorganism is capable of expressing a heterologous protein.

13. (Four Times Amended) A method for the production of a heterologous protein in a transformed *Bacillus subtilis* host cell comprising the steps of:
(c) obtaining a *Bacillus* host cell comprising a nucleic acid encoding said heterologous protein wherein said host cell contains a mutation or deletion in at least one of the genes encoding *B. subtilis* cysteine protease 1, wherein said at least one of the genes encoding cysteine protease 1 encodes the amino acid sequence set forth in SEQ ID NO:2; and
(d) growing said *Bacillus* host cell under conditions suitable for the expression of said heterologous protein.

20. (Amended) The method of Claim 13, wherein said at least one of the genes encoding cysteine protease 1 comprises the nucleic acid sequence set forth in SEQ ID NO:1.

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Please add the following new Claims:

22. A *Bacillus subtilis* cysteine protease-1 encoded by a nucleic acid sequence comprising SEQ ID NO:1.

23. A *Bacillus subtilis* cysteine protease-1 set forth in an amino acid sequence comprising SEQ ID NO:2.